Risk Assessment Document
For
HPHV Steam Sterilizer

RISK ASSESSMENT FOR HPHV STEAM STERILIZER

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1 Introduction:

According to the definition, given in Annex 15 to the EU-GMP-Guide, a Risk Assessment is a method to assess and characterize the critical parameters in the functionality of an equipment or process. Therefore, risk assessment is a key element in the qualification and validation approach.

In the project context, risk assessment for the equipment is performed as basic GMP/ EHS-Risk Assessment, which shall help to identify important GMP/ EHS-requirements.

2 Aim of Risk Assessment:

At the very basic stage of design the Risk Assessment is carried out to verify that all features are taken into consideration to avoid the risk of failure of critical GMP and EHS parameter in the equipment.

During study, all GMP, EHS and operational parameters will be identified and assessed for the risk, appropriate mitigation will be proposed and verification point will be identified and defined.

The Risk Assessment report is produced to provide the documented evidence that design concepts or requirement are complete in considering all GMP, EHS and operational risks.

3 Reference Documents/ Drawings:

S.No.	Document Title	Document Number
1.	Validation master plan	

4 Equipment/ System Description

This risk assessment is conducted for a HPHV Steam Sterilizer, which shall consist of the following main components:

- Sterilization chamber (pressure vessel with external jacket)
- Facing Loading/ unloading side panels
- Two horizontally sliding doors
- Thermal insulation with external sheathing
- Frame for chamber and valves
- Pipes and valves
- Control devices and instrumentation
- Process controller
- Liquid ring vacuum pump system for mechanical air removal
- Intake air filter, equipped with connections suitable to perform manually the WIT test
- Operating panel installed on Non-sterile side
- Printer installed on Non-Sterile side
- Indicators at loading/unloading side
- Temperature probes and pressure transducers
- External/ internal trolley(s)
- Air/ water separator installed on general drain

The unit shall be used for sterilization of garments, machine parts, rubber stoppers, seals and other accessories which are required within the aseptic area.

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The equipment shall be equipped with two horizontally sliding doors. Each door shall be interlocked by motorized cylinder mounted laterally on both side of the door. The sealing of the chamber shall be achieved through the heat resistant food grade silicon gaskets located within the groove between chamber and jacket.

The equipment performs sterilization using dry saturated steam. A well designed jacket shall be provided around the chamber, which shall be used as a heating medium for chamber.

The equipment shall be fully automatic with the use of PLC and MMI.

The Sterilization process shall be designed for:

- Removal of air from Autoclave and load using either dynamic vacuum or vacuum/ steam pulsing.
- Raising the temperature of load to sterilization temperature by injection of steam under pressure, while effectively removing condensate & air pockets.
- Attain uniform penetration of heat throughout Steam Sterilizer chamber and to fulfill equilibrium time criteria of 15/30 seconds (for porous load only).
- Hold the specified temperature for time sufficient to achieve sterility.
- Cool the load to safe handling temperature without damaging physical, chemical composition and sterility.
- Drying the load articles using hot filtered compressed air

Most of the possible risk concerning the handling/ operation of the Steam Sterilizer (Autoclave) has been considered in this RA document.

5 Participants:

Name	Designation/ Department	Signature/ Date

6 Risk Management Process

A typical Risk management process consists of following steps:

- Risk Assessment:
  - Risk Identification
  - Risk Analysis
  - Risk Evaluation

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- Risk Control
  - Risk Reduction
  - Risk Acceptance

- Result of Risk management processes
- Risk Review

- Risk Assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.
  Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description.
  Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harm.

  Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluation considers the strength of evidence for all three of the fundamental questions.
  The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of range of risk. In case of qualitative description the risk is expressed using descriptors such as “high”, “medium” or “low”.

- Risk control includes decision making to reduce and/ or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used of risk control should be proportional to the significance of the risk.
  Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. Risk reduction might include actions taken to mitigate the severity and probability of harm.
  Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified.
- The output/ result of the quality risk management process should be appropriately communicated and documented.
- Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.
- The output/ results of the risk management process should be reviewed to take into account new knowledge and experience.

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  The output/ results of the risk management process should be reviewed to take into account new Knowledge and experience.

  This document applies the risk management principles to identify the risks associated with the design, Construction and operational features of the proposed sterile formulation facility.
  The objectives of this risk assessment are to:
  • Review the design around a structured methodology
  • Identify the failure modes and associated risks
  • Check if the proposed control measures are adequate
  • Identify recommendations to obtain a more acceptable risk level if required.

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6.1 Identifying GMP risk:

Identification of Risk associated with the equipment, is generally based on prior experience and the concerns of the participants of risk assessment document.

The risks identified are categorized as “GMP risk” or “Non-GMP risk”.

GMP is defined as “the practices which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.”

Thus, GMP covers all aspects of the manufacturing process: defined manufacturing process; validated critical manufacturing steps; suitable premises, storage, transport; qualified and trained production and quality control personnel; adequate laboratory facilities; approved written procedures and instructions; records to show all steps of defined procedures have been taken; full traceability of a product through batch records and distribution records; and systems for recall and investigation of complaints.

Thus those risks which might have a direct or indirect impact on the quality of the product are classified as “GMP risk”. Also, those risks which might result in regulatory guidelines non-compliance are also classified as “GMP risk”.
For example: The Hygiene level of the manufacturing areas has a direct impact on the quality of the Product. Thus, it is classified as GMP risk.
The “Non GMP” risks include risks related to EHS, operational and other non-critical hazards.

Following types of risks are mainly identified during risk assessment process:

- Risk related to hygiene level of the manufacturing and supporting areas
- Risks related to appropriate utilities and their control (eg. power source, compressed air etc.)
- Risks related to calibration/ preventive maintenance
- Risks related to protection of the environment and health & safety of personnel.
- Risks related to cleaning & sterilization
- Risks related to unidirectional flow of the material
- Risks related to cross contamination of the products
- Risks related to entry and exit of personnel and material.
- Risks related to all the environment features of the manufacturing areas.
- Risks related to requirement of particular rooms for different activities.
- Risks related to environment health and safety of personnel.

6.2 RISK ANALYSIS & EVALUATION:

The risk analysis is performed using a qualitative basis of approach.

Qualitative analysis uses word form or descriptive scales to describe the magnitude of potential consequences/ impact and the likelihood that those consequences will occur.

The qualitative measures of likelihood includes descriptors like “Unlikely”, “Possible” and “Likely”, whereas the qualitative measures of consequence/ impact includes descriptors like “Minor”, “Moderate” and “Major”.

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Qualitative measures of likelihood

Level	Descriptor	Example detail description
1	Unlikely	May occur at some time
2	Possible	Might occur at some time
3	Likely	Will probably occur in most circumstances

Qualitative measures of consequence/ impact

Level	Descriptor	Example detail description
1	Minor	• No impact on the product quality or outcome of the equipment. • Features required for easing equipment operation.
2	Moderate	• No direct impact on product quality/ outcome of equipment. However may indirectly affect the product quality. • Minor effect on personnel health • Used in the initial stage of operation, however it may affect the final output but those are not used for final release of output. • Effect on environment such as clean room.
3	Major	• Features having direct impact on product quality/ outcome of equipment like contact parts MOC, Surface finish, Control system, Process air quality etc. • Failure could lead to regulatory non-compliance. • Loss/ damage to equipment or its critical sub-components • Critical instruments not calibrated or not of desired range or accuracy. • Proper supporting documentation not provided. • Major effect on personnel health

Based on the above parameters of likelihood and consequence a qualitative risk analysis matrix is prepared to identify the overall Level of Risk, as mentioned in table below.

Qualitative risk analysis matrix – level of risk

Likelihood	Consequences/ Impact		
	1 – Minor	2 – Moderate	3 – Major
1 (Unlikely)	Low	Medium	High
2 (Possible)	Low	Medium	High
3 (Likely)	Medium	High	High

The final Risk level shall thus be described using descriptors such as “Low”, “Medium” & “High”, where each descriptor implies the following meaning:

Low – Risk can be accepted or ignored. These do not affect the final quality of the equipment/ system and it can be managed by routine procedures and are unlikely to need specific application of resources.

Medium – Risk required ongoing monitoring and review, to ensure level of risk does not increase. Otherwise managed by routine procedures.

High – Action plans must be developed, with clear assignments of individual responsibilities and timeframes.

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7 Risk Assessment:

In the following section a table is produced for the risk assessment. The significance or instruction for each column is described in the following paragraph.

Column 1 : **Serial number** of the Risk assessment item

Column 2 : **Process step/ Component**: Identify the process step or component associated with the risk.

Column 3 : **Risks:** Identify the type of risk associated with the process or component

Column 4 : Verify that whether risk have **GMP impact** in terms of Yes/ No.

Column 5 : **Justification:** Provide justification for declaring both Yes/ No for GMP impact in column 4.

Column 6 : For the risk **other than of GMP impact**, write that what is/ are the type of risks e.g. EHS, operational, etc.

Column 7 : **Justification:** Provide justification for considering the risk.

Column 8 : **Risk level:** Determine the risk level as High, Medium or low based on the impact.

Column 9 : **Risk Control:** It is further divided into the following three sections:

Column 9a : **Mitigation Method:** Write the risk mitigation strategy as considered in the design.

Column 9b : **Residual risk level:** After the risk mitigation what is the residual risk level, whether it is Acceptable, Low or Medium.

Column 9c : **Test document:** Write the test point where the risk mitigation strategy will be verified.

Column 10 : **Status of RA:** Mention the status of the Risk assessment point i.e. whether it is ‘Closed” or “Open”, after the execution/ approval of the Test document.

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General Design of Equipment/ Components											
1.	Chamber size	Insufficient space for sterilizing articles	Yes	Adequate space for the operation is a GMP requirement to conduct error free operation	Operational	Load patterns may increase in case chamber size is small.	Medium	▪ The Autoclave size shall be sufficient to cater to the demand of the production load. The size shall be designed considering the load patterns. ▪ Load patterns shall be fixed and qualified.	Acceptable	IQ & PQ	
2.	Sterilization chamber	No test ports / flanges available	Yes	PQ study cannot be performed	No	NA	High	▪ Validation ports shall be provided on the side walls for multi-point temperature mapping. ▪ Access to the validation ports should be possible through the technical area.	Acceptable	IQ	
Chamber											
3.	Sterilization chamber	Chamber cannot be drained completely/ not fully self-draining.	Yes	▪ Accumulation of condensate in parts of equipments, sterilization out of control, risk of contamination, ▪ Complete drainage not possible.	No	NA	High	▪ Design of the chamber shall be appropriate such that slope is provided in the entire chamber towards the drain. ▪ Drain shall be located at the deepest point of the chamber.	Acceptable	IQ	
4.	Sterilization chamber	Leakage (autoclave)	Yes	Sterilization process out of specification; contamination of system/ product possible.	No	NA	High	▪ Chamber leak test cycle (Vacuum and Pressure based) shall be provided in the control system for detecting leakage, along with alarm provision in case of failure. ▪ Leak test cycle shall be performed routinely as per frequency mentioned in SOP.	Acceptable	OQ & SOP	

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5.	Sterilization Chamber	No jacket provided around the chamber	Yes	Difficulty in maintaining uniform temperature conditions inside chamber.	Operational/ EHS	▪ Heat consumption increased. ▪ Heat transmission to the environment increased.	Medium	▪ Jacket shall be provided around chamber to increase heat transfer efficiency & structural strength. ▪ Steam supply shall be provided to the jacket to heat up prior to the heating of chamber, during heating/ sterilization phase. ▪ Temperature sensor and pressure indicator shall be provided in the jacket to monitor the temperature and pressure conditions along with alarm provision in case of low or high temperature and pressure.	Acceptable	IQ & OQ	
6.	Sterilization Chamber	Temperature and pressure not uniform	Yes	▪ Inefficient sterilization ▪ Important parameter for the process.	No	NA	High	▪ The jacket shall be heated up prior to the chamber so as to provide uniform heating. ▪ Temperature probe shall be provided in the jacket to monitor the temperature along with alarm provision in case of low or high temperature. ▪ PRV shall be provided on the pure steam line to chamber to control pure steam supply as per requirement. ▪ PRV shall be provided on the plant steam line to jacket to control plant steam supply as per requirement ▪ Alarm shall be provided in case of low/ high temperature conditions in the jacket or chamber. ▪ Chamber temperature and pressure shall also be continuously monitored by temperature & pressure sensors and alarm shall be provided in case temperature or pressure goes out of set limit. ▪ In case sensors are not working or are faulty, alarm shall be generated. ▪ Routine calibration of the temperature and pressure sensors shall be performed as per SOP.	Acceptable	IQ, OQ & SOP	

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Doors											
7.	Doors	Door sealing damage	Yes	▪ Sterilization out of validated procedure. ▪ Sterilization temperature will not achieve.	No	NA	High	▪ Door sealing failure shall be alarmed. ▪ Manometers shall be installed to monitor door gasket pressure along with alarm in case pressure is low. ▪ Process shouldn't start in case doors are not sealed properly. ▪ Regular visual check and preventive maintenance of the door gasket seal shall be done regularly as per SOP.	Acceptable	IQ & OQ & SOP	
8.	Doors	Door position indicator failure/ damage; Door interlock does not work	Yes	Contamination of clean room possible by simultaneous opening of both doors; sterilization out of validated procedure.	No	NA	High	▪ Alarm provision shall be provided in case door position indicators are not working. ▪ Process shouldn't start until both doors are closed and locked. ▪ Door interlocking feature shall be verified during qualification ▪ The working of door position indicators and interlocking shall be checked regularly as per SOP for Preventive maintenance.	Acceptable	OQ & SOP	
9.	Doors	Door opens with process running or potentially dangerous condition exist inside chamber	Yes	Articles may move with the pressure flow.	EHS	▪ Personnel may be at Risk. ▪ Environment temperature may get increased.	High	▪ Door shouldn't open until potentially dangerous conditions exist within chamber and it should open only once process end/ door opening parameters have been reached. ▪ Door also shouldn't open if any process is running in the chamber.	Acceptable	OQ	
10.	Doors	Door at clean side not locked in case of failed/ aborted sterilization process	Yes	Not sterilized components/ accessories may be unloaded from the sterile side. Clean room contamination possible.	No	NA	High	Sterile side door shouldn't open in case sterilization process is not completed successfully or if process is aborted.	Acceptable	OQ	

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Piping											
11.	Valves for clean media	Valves are not of hygienic/ sanitary design	Yes	Contamination possible	No	NA	High	Valves on clean media line to the chamber should be of hygienic/ sanitary design i.e. diaphragm valves.	Acceptable	IQ	
12.	Piping (Clean steam, & drain)	▪ Inclination of piping too low; stagnant water. ▪ Piping system contains dead legs, air pockets	Yes	▪ Pipelines cannot be drained completely, drain ability not sufficient capacity ▪ Risk of contamination / microbial growth in piping possible	No	NA	High	▪ Clean Steam piping to the chamber and condensate outlet piping from the chamber shall have adequate slope to avoid water clogging in the line and thereby preventing microbial contamination. ▪ No dead legs or air pockets should be present.	Acceptable	IQ	
13.	Piping (Clean steam, & drain)	Welding quality not appropriate	Yes	GMP requirement; Cleaning problems, surface conditions out of specification in case of bad welding quality.	No	NA	High	▪ Orbital welding shall be done for all contact pipings (clean utilities). ▪ Where orbital welding is not possible, manual TIG welds shall be done. ▪ Welding verification reports and welder qualification certificate shall be provided by vendor.	Acceptable	IQ	
14.	Piping (Clean steam, & drain)	Material of pipeline not suitable/ resistant; interaction with media possible.	Yes	Material may react with cleaning media and contaminate the articles to be sterilized.	No	NA	High	▪ All metallic contact materials of clean media piping & chamber shall be made of SS 316 or better. ▪ Non-metallic/ elastomers contact parts shall be made up food grade quality material i.e. silicone, Viton, PTFE etc.. ▪ Material test certificates/ manufacturer's declaration shall be provided for both.	Acceptable	IQ	

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15.	Piping	Water accumulation in drain & chamber	Yes	▪ Inefficient sterilization. ▪ Contamination of the product.	No	NA	High	▪ Adequate piping slope shall be provided to avoid water clogging. ▪ Temperature shall also be continuously monitored in the drain & chamber during process. ▪ Hot Air drying arrangement shall be provided	Acceptable	IQ & OQ	
16.	Drain lines	▪ Drain lines not connected to common header drain. ▪ Steam emission from drain lines. ▪ Back pressure from drain line to the autoclave chamber.	Yes	Clean room temperature and RH conditions may be disturbed from the steam released inside room.	Operational/ EHS	▪ Sterilization process time shall be increased. ▪ Chamber and operator safety at risk due to back pressure.	Medium	▪ All drain lines shall be connected to common header having adequate size to decrease heat-up time. ▪ Drain cooling system shall be installed on the common header drain line to reduce the temperature of the drain to 80˚C, before draining. ▪ A cyclone separator shall be provided on the common header drain line with an air vent to de-pressurize the condensate and generic waste by separating air from the liquid waste and thereby preventing back pressure.	Acceptable	IQ	
Filters											
17.	Filter (Compressed air line)	No sterile filters on compressed air line to chamber.	Yes	Basic requirement for preventing contamination of articles after sterilization.	No	NA	High	Sterilization grade hydrophobic filter (0.2 micron pore size) shall be provided on the vacuum break (Compressed air) line.	Acceptable	IQ	
18.	Filter (Compressed air line)	Filter choking/ leakage	Yes	Chances of contamination of product being sterilized.	No	NA	High	▪ PRV shall be provided in compressed air line to control the pressure as per requirement. ▪ Certification regarding the Integrity testing of the filters shall be provided by the vendor. ▪ Online filter integrity test shall be possible for the filter. ▪ Filter integrity test shall be conducted at	Acceptable	IQ & SOP	

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								regular interval as per SOP. ▪ Regular exchange of filter cartridges as per SOP.			
19.	Filter (Compressed air line)	In-situ sterilization of filter and filter housing is not possible	Yes	Chances of contamination of the compressed air pipelines while removing filter for sterilization; contamination of chamber.	No	NA	High	▪ In-situ sterilization of filter and filter housing should be possible, through automatic filter SIP cycle provided in the control system. ▪ A temperature sensor shall be provided for monitoring of temperature during sterilization cycle of filter.	Acceptable	IQ & OQ	
20.	Filter (Compressed air line)	Affected by the high temperature and pressure during the sterilization process	Yes	Filter efficiency will decrease leading to further contamination of the articles under sterilization.	No	NA	High	▪ Sterilizable grade filter should be used. ▪ Provision shall be incorporated in the SOP to check the efficiency of the filters at regular intervals. ▪ Filter shall be replaced after set number of sterilizable cycle, as mentioned in SOP.	Acceptable	IQ & SOP	
21.	Filter (Compressed air line)	Filter housing drain ability is not sufficient	Yes	Water stagnation in Filter housing; chances of microbiological contamination	No	NA	High	▪ The filter housing shall be self-draining type. ▪ Proper slope shall be provided on the drain line of filter housing.	Acceptable	IQ	
System Functions											
22.	Loading/ Unloading	Loading/ Unloading of the articles inside autoclave chamber is not GMP compliant	Yes	Loading will lead to the violation of the GMP.	No	NA	High	▪ Loading of the articles shall be done using SS 304 transfer trolleys; articles for sterilization shall be placed on internal trolley of MOC SS 316 or better. ▪ Internal trolley shall have adjustable perforated SS shelves.	Acceptable	IQ	

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23.	Loading/ unloading position of autoclave/ trolley	Inoperability or safety risk for operator	Yes	Loading level/ system between autoclave and trolley not appropriate	No	NA	Medium	The design of autoclave and trolley shall be verified, during installation and both should be on the same loading level.	Acceptable	IQ	
24.	Loading	Loading scheme not defined / wrong	Yes	Sterilization out of validated procedure	No	NA	High	▪ Loading scheme shall be defined and validated during PQ study. ▪ SOP 'Operation of the Autoclave' shall mention the validated load patterns.	Acceptable	PQ & SOP	
25.	Heating	Heating time too long	Yes	Cycle-time increases, negative influence on heat sensitive articles possible	No	NA	High	▪ Alarm provision shall be provided in case of too long heating time. ▪ Heating time too long set point, shall be verified based on proper process designing to have optimum and reproducible heat up time.	Acceptable	OQ & PQ	
26.	Sterilization	Temperature too high/ temperature overshoot during sterilization hold.	Yes	Negative influence on heat sensitive media / goods; Sterilization process out of validated procedure.	No	NA	High	▪ Alarm provision for high temperature during sterilization hold i.e. higher than set value. ▪ Pure steam supply to chamber shall stop in case of temperature overshoot.	Acceptable	OQ	
27.	Sterilization	Temperature too low during sterilization hold	Yes	Sterilization process out of validated range	No	NA	High	▪ Alarm provision for temperature lower than set value during sterilization hold. ▪ The sterilization timer should stop in case chamber temperature goes below the sterilization temperature for some settable time period and restarts from the same point if the temperature is achieved within the time period. ▪ The sterilization timer should reset, if chamber temperature doesn't reaches sterilization hold set point within settable time period.	Acceptable	OQ & PQ	

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								▪ The settable time period shall be decided after qualification.			
28.	Sterilization	Chamber or Jacket pressure too high	Yes	▪ Sterilization process out of range. ▪ Goods may be damaged.	Safety	Safety risk to operator	High	▪ PRV shall be provided in plant steam & pure steam line to control the pressure as per requirement. ▪ Alarm provision shall be provided in case of high chamber or jacket pressure. ▪ Pure steam supply to the chamber and plant steam supply to the jacket turns off in case of high pressure. ▪ Safety relief valves shall be provided in case pressure goes above set value.	Acceptable	OQ	
29.	Sterilization	Sterilization hold time too short	Yes	Goods not sterile	No	NA	High	▪ Sterilization fail message shall be displayed and printed in case sterilization hold time is less than set hold time or the target F0 value is less. ▪ Appropriate program design shall be done during qualification. ▪ Temperature mapping shall be done during qualification to study sterilization hold time achieved. ▪ Biological indicator challenge test shall be performed during qualification for all loads.	Acceptable	OQ & PQ	
30.	Sterilization	Presence of Non condensable gases.	Yes	Sterilization will not be proper, Goods are not sterilized.	No	NA	High	▪ Sampling valve shall be provided in pure steam line to check the pure steam quality. ▪ Quality of pure steam shall be checked during qualification studies & regularly as per SOP.	Acceptable	IQ, OQ & SOP	

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31.	Sterilization	Incorrect temperature & pressure measurement	Yes	Sterilization out of validated procedure	No	NA	High	▪ Temperature and pressure sensors should be calibrated. ▪ The system shouldn't take the reading of temperature and pressure sensor in case the reading is out of settable limit, in case of any fault in sensors. ▪ Alarm shall be generated in case of faulty sensor. ▪ Routine calibration of sensors shall be performed as per SOP for Calibration.	Acceptable	IQ, OQ & SOP	
32.	Sterilization	Articles will remain under the High temperature & High pressure influenced environment, even after the sterilization process is over.	Yes	Excess exposure to such environment will influence the product.	No	NA	High	▪ Chamber exhaust valve should open automatically once the process ends. ▪ A safety thermometer connected to an independent chamber temperature probe and equipped with independent digital display, shall be provided for monitoring chamber temperature. It should prevent opening of the doors in case of too high temperature in the chamber. ▪ Cooling cycle shall be provided in the end of the process so as to cool down the load gradually using compressed air inside chamber and water circulation in jacket, and prevent damage to containers. ▪ Audio/ visual alarm shall be provided to assure that the process had completed once settable parameters have been reached.	Acceptable	IQ & OQ	
33.	Cooling	Cooling process after sterilization not available	Yes	For articles sterilized at low temperature may not sustain high temperature conditions after sterilization.	No	NA	High	A rapid cooling phase shall be provided after sterilization wherein, chilled soft water shall be circulated in the jacket for rapid cooling of the chamber.	Acceptable	OQ	

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34.	Cooling	The temperature of soft water circulated in jacket for cooling is high.	Yes	Cooling will not be proper; shall take too long time	No	NA	High	▪ A heat exchanger with chilled water supply shall be provided at the soft water discharge line for chilling of soft water. ▪ The flow of chilled water shall be controlled based on the temperature requirement of soft water. ▪ Thermostat shall be provided to maintain temperature of soft water.	Acceptable	IQ & OQ	
35.	Cooling	Soft water required for cooling is low in quantity/ pressure.	Yes	Cooling process shall be affected	No	NA	High	▪ Soft water tank shall be provided for storing of soft water, along with level switches to maintain the required amount of soft water in tank. ▪ A discharge pump shall be provided at the outlet of the tank to discharge soft water to jacket, at set pressure. ▪ The pump operation shall be interlocked with soft water level inside tank and stops in case of low level.	Acceptable	IQ & OQ	
36.	Sterilization	Cold spots due to incomplete displacement of air	Yes	Air pocket formation inside chamber; Sterilization process insufficient	No	NA	High	▪ Pre-sterilization vacuum cycle shall be provided in the process to remove any residual air prior to heating, thereby preventing formation of any air pockets. ▪ Pulsing cycle provision shall be provided for pre-sterilization vacuum cycles to increase efficiency of residual air removal. ▪ Vacuum pump should remain continuously on during pre-pressurizing stage so as to remove any residual air through reduced size valve. ▪ Air detector system shall be provided for detecting any residual air in the chamber during the process. ▪ Alarm provision shall be provided in case residual air is detected inside chamber and the sterilization process shall be failed/ invalidated.	Acceptable	IQ, OQ & PQ	

RISK ASSESSMENT FOR HPHV STEAM STERILIZER

S.No. (1)	Process steps/ component (2)	Risk (3)	GMP Risk Yes/ No (4)	Justification (5)	Other Risk type (6)	Justification (7)	Risk Level (8)	Risk Control (9)			Status of RA (10)
								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
								▪ Temperature mapping of the chamber shall be performed to identify "cold spot' and to ensure that it meets required sterilization process conditions.			
37.	Pre and Post vacuum phase	Vacuum pump fails	Yes	Pre-pulsing & Drying out of validated procedure	No	NA	High	▪ Pressure of the chamber shall be continuously monitored through pressure transmitter. ▪ Alarm shall be provided in case vacuum pump fails or in case vacuum is not attained within required time. ▪ Regular maintenance of vacuum pump shall be done as per preventive maintenance SOP.	Acceptable	IQ, OQ & SOP	
38.	Vacuum level	Required amount of vacuum is not achieved	Yes	Pre-pulsing & Drying out of validated procedure	No	NA	High	▪ Soft water at low temperature shall be provided to the vacuum pump inlet. ▪ A heat exchanger with chilled water supply shall be provided at the soft water supply line for chilling of soft water. ▪ Pump shall be provided to circulate soft water with constant flow. ▪ Flow switch should be provided in line.	Acceptable	IQ & OQ	
39.	Vacuum	Soft water required for vacuum pump is low in quantity/ pressure.	Yes	Pre-pulsing & Drying out of validated procedure	No	NA	High	▪ A soft water tank shall be provided for storing of soft water, along with level switches to maintain the required amount of soft water in tank. ▪ Vacuum pump operation shall be interlocked with soft water level inside tank such that it stops in case of low level.	Acceptable	IQ &OQ	
40.	Drying with vacuum and post sterilization heating	Goods not dry	Yes	▪ Re-contamination/ microbial growth possible. ▪ Articles may not be suitable for manufacturing. .	No	NA	High	▪ Proper post sterilization vacuum cycle shall be provided. ▪ Filtered hot air drying phase option shall be provided after sterilization to dry the load articles.	Acceptable	IQ, OQ & PQ	

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
								▪ Heat exchanger shall be provided on the compressed air line to the chamber, with steam supply, to heat the compressed air for drying. ▪ Temperature sensor shall also be provided after heat exchanger to monitor the air temperature and regulate steam supply to the heat exchanger as per set temperature. ▪ Garments/ goods dryness test shall be a part of qualification study.			
41.	Sterilization	Fluctuations in temperature during sterilization hold phase; temperature not maintained within sterilization band.	Yes	Sterilization process out of validated procedure	No	NA	High	▪ Multipoint temperature mapping shall be done inside the autoclave chamber and drain line to control so as to maintain uniform temperature and pressure conditions inside the chamber. ▪ PRV shall be provided at pure steam inlet to the chamber, which shall control steam inlet based on the pressure set point, thereby controlling temperature within specified parameters. ▪ The system shall be designed to provide a temperature accuracy of ±0.5˚C throughout chamber during sterilization hold. ▪ Temperature mapping shall be carried out during qualification study to validate the same.	Acceptable	IQ, OQ & PQ	
Equipment Construction											
Internal Surface											

RISK ASSESSMENT FOR HPHV STEAM STERILIZER

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
42.	Sterilization Chamber inclusive doors and connected parts/ equipment in direct contact with chamber, piping	The material of internal surface such as sterilization chamber including doors and connected parts/ contact parts is not suitable.	Yes	MOC not resistant - Interaction with product possible	No	NA	High	▪ Metallic critical contact surfaces shall be constructed of 316 grade stainless steel or better, electro polished, orbitally welded. ▪ The suitability of the materials shall be proven by certificate/ manufacturers declarations. ▪ Supporting structure and non-contact parts shall be made up of SS 304 or better.	Acceptable	IQ	
43.	Polymeric materials	Polymeric materials are not compatible and are not replaceable	Yes	May lead to indirect contamination of product.	No	NA	High	▪ Gaskets and O-rings coming in direct/ indirect contact surfaces of clean utility pipelines/ chamber shall be made up of food grade polymeric materials only and shall be high temperature and pressure resistant. ▪ Easy change of gaskets should be possible. ▪ Food grade polymeric material certificate/ declaration have to be provided by vendor.	Acceptable	IQ	
44.	Welding Joints	Weld joints not grounded properly and are not passivated	Yes	Uneven and improperly ground weld joints will form a space for dust accumulation	No	Na	High	▪ All welds shall be orbitally welded, ground finished and properly labelled with ID No., passivated ▪ 100% Boroscopy shall be performed. ▪ Manual TIG welding should be performed, where orbital welding is not possible. ▪ Boroscopy CD/ Weld reports/ certificate/ declaration have to be provided by vendor.	Acceptable	IQ	
45.	Sterilization Chamber inclusive doors and connected parts / equipment in direct contact	Surface finishing insufficient	Yes	May lead to improper cleaning of the surface which will lead to microbial growth or particulate contamination.	No	NA	High	▪ Internal surface roughness, Ra ≤ 0.8 µm, proven by certificates/ declaration for metal parts. ▪ Crevice free smooth, rounded corners & smooth surface.	Acceptable	IQ	

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
	with chamber, piping										
External Surface											
46.	Surface	External surface of equipment is not suitable	Yes	May lead to the clean room contamination	No	NA	Medium	Supporting structures and frames installed inside clean rooms shall be made up of SS 304 or better grade stainless steel.	Acceptable	IQ	
47.	Finishing	External finish of equipment is not proper.	Yes	May lead to the microbial growth	No	NA	Medium	External surface should be free from sharp edges, corners, crevices etc., all metallic external surface shall be matt or mirror finished.	Acceptable	IQ	
Utilities											
48.	Pure steam pressure to chamber	Steam quality not adequate / steam pressure conditions not adequate.	Yes	Sterilization out of validated procedure	No	NA	High	▪ PRV/ Pressure switch/ transmitter shall be provided at pure steam inlet line for monitoring and controlling of steam pressure, along with alarm provision. ▪ Pure Steam supply to the equipment shall be qualified.	Acceptable	IQ & OQ	
49.	Pure Steam	Too much condensate in the pure steam supply to the chamber	Yes	▪ Pure Steam heating capacity shall be decreased. ▪ Goods shall become wet. ▪ Sterilization cycle out of validated procedure.	No	NA	High	Moisture separator along with Steam trap assemblies shall be installed at the pure steam supply at suitable points.	Acceptable	IQ	
50.	Soft Water	Low/ No soft water for vacuum pump and jacket cooling	Yes	Inefficient vacuum level & jacket cooling; sterilization process out of validated procedure.	No	NA	High	Pressure switch/ transmitter shall be provided at Soft water inlet line along with alarm provision in case of low pressure.	Acceptable	IQ & OQ	

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
51.	Chilled Water	Low/ No chilled water for the process	Yes	Chamber cooling process after sterilization shall be affected.	No	NA	High	Pressure switch/ transmitter shall be provided at Chilled water inlet line along with alarm provision in case of low pressure.	Acceptable	IQ & OQ	
52.	Plant steam	Low/ No plant steam for the jacket	Yes	Sterilization cycle out of validated procedure	No	NA	High	PRV/Pressure switch shall be provided at Plant steam line along with alarm provision in case of low or No pressure.	Acceptable	IQ & OQ	
53.	Compressed air	Insufficient pressure	Yes	Equipment operation will be disturbed	No	NA	High	PRV/ Pressure switch/ transmitter should be provisioned at compressed air inlet to monitor & control compressed air pressure along with alarm provision.	Acceptable	IQ & OQ	
Cleaning											
54.	Cleaning	Difficulty in cleaning due to improper design of complete equipment.	Yes	Accumulation of particles, contamination of articles orr clean room possible	No	NA	High	▪ The design of the complete equipment shall ensure adequate clean ability (smooth, SS 316/ 304 or better surface). ▪ All bolts, nuts on the exterior part of equipment shall be of clean room design, for e.g. provided with dome nuts, etc.	Acceptable	IQ	
55.	Labeling of components	Labeling of components/ media inappropriate	Yes	Prerequisite for qualification & maintenance	No	NA	Medium	▪ Unique identity number/ flow direction should be provided on components/ media, operator panel, etc. (e.g. according to P&ID) ▪ Labels affixed on the equipment should be heat resistant. ▪ All labelling shall be done in English language and according to P&ID.	Acceptable	IQ	
PLC/ Control System											

RISK ASSESSMENT FOR HPHV STEAM STERILIZER

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
56.	Process automation	Process parameters are not controlled automatically.	Yes	Possibility of human error leads to a process which is not validated	No	NA	High	▪ The System shall be PLC based and fully automatic. ▪ The equipment shall control & detect failure mode automatically.	Acceptable	IQ & OQ	
57.	Man-machine Interface	Process / process status not visible for operating personnel.	Yes	Operating personnel must have knowledge on the process status	No	NA	High	MMI shall be provided with adequate display and clean room suitable key board/ Touch screen for operation and entering process parameters.	Acceptable	IQ	
58.	Man-machine Interface	Display language not identified.	Yes	Pre-requisite for the GMP compliant operation	No	NA	High	The language on the display of MMI shall be English language.	Acceptable	OQ	
59.	Man-machine Interface	Monitoring of GMP relevant data not possible	Yes	Basic GMP requirement	No	NA	High	▪ Monitoring of GMP relevant data should be possible. ▪ Printout facility shall be available with fade proof prints.	Acceptable	OQ	
60.	Man-machine Interface	Recorder failure	Yes	Basic GMP requirement; Critical process parameters & batch report might not be saved and printed.	No	NA	High	▪ Data backup for process data shall be provided (electronic recording, 21 CFR part 11 compliant). ▪ Diagnostic function test for the same shall be carried out as part of qualification activity. ▪ Routine backup for process data shall be performed as per SOP.	Acceptable	OQ/ PLC Validation & SOP	
61.	PLC/ Control system	Control system does not detect failures and generate alarms	Yes	Process optimization and validation is not possible	No	NA	High	▪ Failure of set parameters should get indicated as alarms and necessary interlocks should be in place. ▪ Alarm shall be provided in case any critical instrument/ sensor is not working properly, loss of communication or broken wire. ▪ Batch records / print outs shall be defined during qualification.	Acceptable	OQ & PQ	

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
62.	PLC / Control system	Power failure/ emergency stop	Yes	Process out of specification	Safety	Unsafe if start automatically on restoration of power	High	▪ Operator settings shall remain unchanged and restored after emergency stop/ power failure; ▪ Alarm message; ▪ On power failure equipment should come to rest to protect operator, equipment itself & the articles. ▪ Provision of UPS to the control system. ▪ Machine shouldn't start automatically without operator intervention after incident. ▪ SOP for "Operation and Maintenance of HPHV Steam Sterilizer" should mention action to be taken in case of power failure.	Acceptable	IQ, OQ & SOP	
63.	PLC / Control system	Status parameters not clear	Yes	Process for the particular product at particular stage can't be regulated easily.	No	NA	High	▪ Status parameters should remain displayed at each process stage. ▪ Alarm shall also be visualized along with the fault displayed.	Acceptable	OQ	
64.	Accessibility to PLC	Parameter settings not identified universally	Yes	Basic GMP requirement	No	NA	High	Parameters settings shall be in numeric only.	Acceptable	OQ	
65.	PLC / Control system	Malfunction of control system	Yes	Correct function of control system is a basic requirement for GMP-compliant operation	No	NA	High	▪ Input/ Output test implementation during qualification activities ▪ The system should contain all necessary protection devices to ensure that the equipment and article remain in safe condition. ▪ Control system software backup should be provided by the vendor.	Acceptable	OQ	

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
66.	PLC / Control system	Time measurement works incorrect	Yes	Process cannot be carried out using validated parameters.	No	NA	High	▪ PLC Clock verification shall be performed during qualification. ▪ Time synchronization of system clock shall be done with centralized server clock. ▪ Time verification of the system clock shall be performed at frequent intervals as per SOP.	Acceptable	OQ & SOP	
67.	PLC / Control system	The machine operates in same manner, even when the different task is required.	No	No impact on sterilization process or components.	Operational	Wastage of the utilities, not required in the operation.	Medium	▪ PLC shall be equipped a minimum of following different cycles - ➢ Chamber Leak test cycle. ➢ Hot Leak Test ➢ Chamber Pressure Leak Test ➢ Bowie Dick Test ➢ HPHV process with hot air drying ➢ Standard process for liquid load with cooling. ➢ Heating and sterilization of air filter and final hot air drying. ▪ Creation and saving of multiple recipes for each sterilization process should be possible.	Acceptable	OQ	
68.	PLC / Control system	No protection of PLC against manipulation & changes.	Yes	Basic GMP requirement.	No	NA	High	▪ Minimum 3 level password protection shall be provided for the system. ➢ Level 1: Operator ➢ Level 2: Supervisor ➢ Level 3: Admin/ Manager ▪ System shall allow only authorized users to access system and change parameters. ▪ All users shall be provided with unique passwords. ▪ Audit trail facility shall be provided for the control system.	Acceptable	OQ	
Measuring Instruments											

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
69.	Measuring Instruments	Measuring Instruments not suitable	Yes	Improper measurements	No	NA	High	▪ Measuring Instruments installed should have suitable measuring range. ▪ Operational range of measuring instruments shall be greater than equipment's working range. ▪ Measuring Instruments should have appropriate accuracy.	Acceptable	IQ	
70.	Measuring instruments	Measuring instruments not calibrated	Yes	Non-calibrated measuring instruments may lead to false machine functions	No	NA	High	▪ Measuring instruments shall be calibrated, traceable to national or international standards. ▪ Re-calibration of instruments should be possible.	Acceptable	IQ	
71.	GMP relevant measurement instruments	Instruments cannot be dismounted	Yes	Defective instruments must be dismounted for exchange and calibration	No	NA	High	▪ Mounting of instruments should give the possibility for dismounting and replacement. ▪ Constructional solution: easy access for re-calibration activities shall be provided.	Acceptable	IQ	
Maintenance											
72.	Maintenance	Malfunctions due to worn parts	Yes	Basic GMP requirement	No	NA	High	▪ Machine shall be easy to maintain. ▪ Preventive maintenance procedure shall be provided by the vendor. ▪ The unit should contain necessary protection devices to ensure that the equipment & the article remain in a safe condition. ▪ Preventive maintenance SOP shall be prepared.	Acceptable	IQ & SOP	
73.	Pumps	Pumps failure (Vacuum pump, Recirculation pump and Soft water discharge pump)	Yes	Sterilization process will be affected.	No	NA	High	Alarm shall be provided in case any pump overload/ trips.	Acceptable	OQ	
Environment & Safety											

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
74.	Electrical system	▪ Electrical systems are not verified for safety. ▪ Earthing not provided for equipment.	No	It will not affect the sterilization process	EHS	May lead to an accident	Medium	▪ All electrical systems shall be tested for safety and shall be provided with safety markings e.g. C.E. marking. ▪ Electrical parts shall be covered. Proper earthing shall be provided for the equipment.	Acceptable	IQ	
75.	Emergency stop	Instantaneous stopping of the equipment not possible	No	Does not have any impact on quality of the product	EHS	Emergency stop function is required for equipment, personnel and product protection	High	Emergency stop shall be installed on accessible area, along with alarm provision.	Acceptable	IQ & OQ	
76.	Noise level	More noise is produced by the equipment during the operation.	No	Does not have any impact on quality of the product	EHS	High noise may cause deafness and anxiety	Medium	Noise level shall be below 75 db at a distance of 1 m from the equipment.	Acceptable	OQ	
77.	Moving & electrical parts	Moving & electrical parts are not covered.	No	Does not have any impact on quality of the product	EHS	Operator safety	Medium	▪ All moving & electrical parts shall be covered properly. ▪ Warning stickers should be affixed on all moving components.	Acceptable	IQ	
78.	Door movement	Some material is stuck in between doors while closing	No	No impact on components, as process will not start until doors are properly closed.	Safety	Safety risk to operator or damage to article which is stuck in between	High	▪ The door closing buttons shall be provided on both sterile and non-sterile sides and doors should be closed only when the button is kept pressed. If button is released the door shall reverse its movement and reopens. ▪ Photocells shall be provided at the end portion of door movement to reverse door movement in case something is stuck in between while door closing.	Acceptable	IQ& OQ	
79.	Autoclave wall	Leakage in wall in which sterilizer is integrated, between clean room class C and class A/B area	Yes	Clean room contamination possible.	No	NA	High	Bio-seal barrier panel shall be installed between sterile room side and non-sterile side to provide leak proof seal.	Acceptable	IQ	

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
80.	Heating	Excess heating & Excess pressure	No	Doesn't have any impact on quality of the product.	EHS	Environmental & operator safety hazards.	Medium	▪ Temperature & Pressure limit for the resistance of the equipment shall be defined. ▪ A safety thermometer, connected to independent chamber temperature probe & equipped with independent digital display shall be provided. If during process, the temperature in chamber goes above safety temperature (max. set level), the thermometer shall lock pure steam & compressed air supply to the chamber. ▪ Elevated pressure in chamber or jacket shall be alarmed leading to the opening of the safety valve and closing of steam and compressed air inlet valve. ▪ Warning stickers on all hot surfaces shall be provided to protect personnel, product and equipment.	Acceptable	IQ & OQ	
81.	Pure Steam/Plant Steam	High Pure Steam /plant steam Pressure	Yes	Sterilization out of validated procedure	EHS	Environment & Personnel safety hazards	High	▪ Pressure regulated valve shall be installed on pure steam & Plant steam inlet line. ▪ Pressure gauge shall be provided on pure steam & plant steam inlet line for monitoring. ▪ Safety valve shall be provided in chamber & jacket in case of high plant steam & pure steam pressure.	Acceptable	IQ	
82.	Heating	High emission of heat	Yes	Disturb clean room temperature.	EHS	Environment & Personnel safety hazards	High	▪ Complete insulation shall be provided around chamber. ▪ SS 304 cladding shall be provided over complete insulation. ▪ The design shall ensure that the temperature on the external surface is NMT 55˚C.	Acceptable	IQ & OQ	

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								Mitigation Method (9a)	Residual risk level (9b)	Test Document (9c)	
83.	Insulation	Insulation material not suitable	Yes	Leads to contamination	No	NA	High	Insulation material used shall be rock wool and covered with completed welded SS304 cladding.	Acceptable	IQ	
84.	Utility	Failure of utility supply is not indicated	Yes	Process parameters may get disturbed	EHS	High pressure may cause accident	High	▪ Various utilities like compressed air supply, pure steam, plant steam, chilled water and soft water are interlocked with the process and any failure is indicated by alarm. ▪ Process shouldn't start if any utility is not available.	Acceptable	OQ	
Documentation											
85.	User	Faulty operation & maintenance	Yes	SOPs are basic GMP-requirement	No	NA	High	▪ All end-users have to be trained on SOPs. ▪ Training of SOPs has to be documented. ▪ Training on the job of end users by vendor. ▪ Training on operation, setting parameters, troubleshooting & maintenance related activities.	Acceptable	PQ & SOP	
86.	User	Operation SOP does not contain proper information and user may operate system.	Yes	User may make a wrong decision.	No	NA	High	▪ System operation SOP shall be reviewed with all aspects and approved. ▪ Vendor support shall be taken for completion of all stages of the qualification.	Acceptable	OQ	
87.	User	Unauthorized person tries to start/stop the system	Yes	Untrained persons may damage the system or product quality may be affected.	No	NA	High	▪ System shouldn't start without password. ▪ Physical entry to equipment room shall be restricted OR ▪ Key switch should be provided for operation of the system	Acceptable	IQ & OQ	

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88.	Vendor	Technical documentation from vendor not adequate	Yes	Adequate technical documentation is basic GMP requirement	No	NA	High	Following documents shall be provided by vendor (in English): ▪ DQ/ FS, IQ and OQ documents ▪ Welding certificates/ declaration along with welder qualification certificate. ▪ Material certificates & surface finish reports ▪ O&M manual ▪ Calibration certificates of all instruments ▪ Bought out components manual ▪ Software backup ▪ Parts list (sufficient details - part no., supplier, type etc.) ▪ Drawings (P&ID, GA, Power wiring etc.). ▪ Certificates of bought out components. ▪ Filter certificates ▪ Hydrotest certificates ▪ Disaster recovery procedure	Acceptable	IQ	

8 Summary & Conclusion:

- The Risk Assessment was performed to establish the design parameters of the equipment so as to meet the desired performance of the equipment i.e. Steam Heat Sterilizer (Autoclave).
- The critical risks pertained to GMP and other than GMP, were analyzed with justification and mitigation procedures.
- For each recognized GMP-risk and other than GMP risks, necessary measures are defined. Organizational measures, like SOPs, are also possible measures for special GMP-risks. The availability of these SOPs will be checked during the performance of the OQ.
- The risks where conceptual procedures shall be employed, standard operating procedures (SOPs), Preventive maintenance schedules, Certificates and related documents indicated as mitigation procedures shall be ensured at respective test points

*"It is concluded that the **Risk Assessment** performed for the equipment will prevent the risk of failures of critical parameters during, design commissioning, installation, operation and performance of the equipment".*

9 Abbreviations:

EU-GMP	:	European – Good Manufacturing Practice
EHS	:	Environment Health Safety
PID	:	Proportional Integral Derivative
TIG	:	Tungsten Inert Gas
GMP	:	Good Manufacturing Practice
PTFE	:	Polytetrafluoroethylene
HPHV	:	High Pressure High Vacuum
SIP	:	Sterilization in place
RA	:	Risk Assessment
Ra	:	Roughness Average
P&ID	:	Process/ Piping & Instrumentation Diagram
PLC	:	Programmable Logic Controller
MMI	:	Man Machine Interface
CFR	:	Code of Federal Regulations
UPS	:	Uninterrupted Power Supply
CE	:	Conformité Européene
db	:	Decibel
DQ	:	Design Qualification
FS	:	Functional Specification
IQ	:	Installation Qualification
OQ	:	Operational Qualification
PQ	:	Performance Qualification
O&M	:	Operation and Maintenance
GA	:	General Arrangement

10 Revision History

Date	Revision	Reason for Revision